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Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/035604 A3

(54) Title: SPLEEN TYROSINE KINASE CATALYTIC DOMAIN:CRYSTAL STRUCTURE AND BINDING POCKETS THEREOF

(57) Abstract: The present invention provides crystalline molecules and molecular complexes that comprise binding pockets of Sykcat and its homologues. The invention also provides crystals comprising the catalytic domain of Syk protein. The invention further provides a computer comprising a data storage medium encoded with the structure coordinates of Sykcat binding pockets and methods for using a computer to evaluate the ability of a chemical entity or compounds to bind to a crystalline molecule or molecular complex of the invention. This invention also provides methods of using the structure coordinates to solve the structure of homologous proteins or protein complexes. The invention further provides methods of using the structure coordinates to screen for, design and optimize chemical entities or compounds, including inhibitory compounds, that bind to the catalytic domain of Syk or homologues thereof.

Published:
— *without international search report and to be republished upon receipt of that report*

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/32812

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C12Q 1/48; C12N 9/12; G06F 19/00
US CL : 435/15, 194; 702/27
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/15, 194; 702/27

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LAW et al. Molecular cloning of human Syk. J. Biol. Chem. 22 April 1994, Vol. 269, No. 16, pages 12310-12319, see the abstract.	1-20 and 32-36
Y,E	JIN et al. The three-dimensional structure of the ZAP-70 kinase domain in complex with staurosporine. J. Biol. Chem. 8 October 2004, Vol. 279, No. 41, pages 42818-42825, see abstract.	1-20 and 32-36
Y,E	WO 2004/029236 A1 (NOVARTIS PHARMA GMBH) 8 April 2004 (08.04.2004), see abstract.	1-20 and 32-36
Y	US 5,130,105 A (CARTER et al.) 14 July 1992 (14.07.1992), see the abstract.	1-20
Y	MCDONALD et al. Crystal Structure of dimeric human ciliary neurotrophic factor determined by MAD phasing. EMBO J. 1995, Vol. 14, No. 12, pages 2689-2699, see abstract.	
Y	MAKINO et al. Automated flexible ligand docking method and its application for database search. J. Comp. Chem. 1997, Vol. 18, No. 17, pages 1812-1825, see abstract.	32-36

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 December 2004 (21.12.2004)	15 FEB 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Nashaat T. Nashed, Ph. D. *T. Roberts for* Telephone No. (571) 272-1600

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PCT/US03/32812

INTERNATIONAL SEARCH REPORT

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TAPIA et al. Computer assisted simulations and molecular graphics. Method in molecular design. 1. Theory and application to enzyme active-site drug design. Molecular Engineering 1994, Vol. 3, pages 377-414, see the entire document.	32-36
A	YAMAMOTO et al. Development of high-throughput fluoroimmunoassay for Syk kinase and Syk kinase inhibitors. Analy. Biochem. 2003, Vol. 256, pages 256-261.	32-36
A	FUTTERER et al. Structural bases for Syk tyrosine kinase ubiquity in signal transduction pathways revealed by the crystal structure of its regulatory SH2 domains bound to a dually phosphorylated ITAM peptide. J. Mol. Biol. 1998, Vol. 281, 523-537, the entire document.	1-20 and 32-36
A	WOODSIDE et al. The N-terminal SH2 domain of Syk and ZAP-70 mediated phosphotyrosine-independent binding to integrin beta cytoplasmic domain. J. Biol. Chem. 18 October 2002, Vol. 277, No. 42, pages 39401-39408.	1-20 and 32-36
A	VIHINEN et al. Structural aspects of signal transduction in B-cell. Crit. Rev. Immun. 1996, Vol. 16, pages 251-274.	1-20 and 32-36

Continuation of B. FIELDS SEARCHED Item 3:
STN SEARCH: Medline, Caplus, Scisearch, Lifesci, Biosis, Embase. WEST SEARCH: PGPB, USPT, EPAB, JPAB, DWPI, USOC. Sequence search of SEQ ID NO: 1, 2, and 5-10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US03/32812

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-20 and 32-36

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.